(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

10/552599

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 October 2004 (21.10.2004)

PCT

(10) International Publication Number
WO 2004/089343 A1

(51) International Patent Classification[7]: A61K 9/20, 31/155, 31/196, 31/198, 31/64

(21) International Application Number: PCT/IB2004/001104

(22) International Filing Date: 8 April 2004 (08.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
591/DEL/2003 9 April 2003 (09.04.2003) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: WATER SOLUBLE TABLETS

(57) Abstract: The present invention relates to water-soluble tablets that dissolve to form clear aqueous solutions, and processes for their preparation. The tablet includes (a) at least one water-soluble active ingredient; (b) one or more water soluble sugar alcohols; (c) one or more water-soluble lubricants; and (d) one or more pH modifiers. The tablet dissolves in less than about three minutes in less than about 30 ml of water to give a clear solution

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WATER SOLUBLE TABLETS

Field of the Invention

The present invention relates to water-soluble tablets that dissolve to form clear aqueous solutions, and processes for their preparation.

Background of the Invention

It has been observed that patient compliance is often reduced due to the inconvenience caused in swallowing conventional dosage forms. Some currently available dosage forms are too large to be swallowed by the elderly or children, and in many cases the patient's ability to swallow a tablet or capsule of any size is compromised. Currently, the available dosage forms that are intended to resolve the issue of compliance and convenience include dispersible tablets, effervescent tablets, and mouth dissolving tablets.

Dispersible tablets are dispersed in water prior to dosing and the suspension formed then is consumed by the patient. Although convenient, the suspension gives the feeling of grittiness in the mouth due to the presence of water insoluble excipients, such as disintegrants. Moreover, there is the possibility of dose loss because the active ingredient may get trapped in these insoluble excipients.

Another dosage form, the effervescent tablet, in addition to the problems associated with dispersible tablets, has the problem of stability. These dosage forms contain an acid/base couple to produce effervescence. In the presence of water, these ingredients react to produce carbon dioxide and effervescence. During the process of manufacture, care must be taken to avoid contact with moisture. This dosage form requires special manufacturing facilities in order to maintain conditions of low relative humidity and low temperatures, which subsequently increases costs and overhead. Additionally, effervescent tablets require special packaging to avoid any moisture absorption during storage. These requirements make the manufacturing of effervescent dosage forms complicated and undesirable.

U.S. Patent No. 3,692,896 discloses the preparation of a water-soluble tablet by direct compression. The tablet includes a water-soluble active ingredient, lactose, and micronized polyethylene glycol as a lubricant. Lactose undergoes a Malliard reaction in the presence of free amines and as a result slows the disintegration of the tablet.

Most active ingredients tend to have an unacceptable taste that becomes more prominent when administered in solution form. Therefore, there is an unmet need for a dosage form that effectively taste masks the active ingredient without decreasing patient compliance.

Summary of the Invention

In one general aspect there is provided a water-soluble tablet. The tablet includes (a) at least one water-soluble active ingredient; (b) one or more water soluble sugar alcohols; (c) one or more water-soluble lubricants; and (d) one or more pH modifiers. The tablet dissolves in less than about three minutes in less than about 30 ml of water to give a clear solution.

Embodiments of the tablet may include one or more of the following features. For example, the tablet may dissolve in water within two minutes or one minute to give a clear solution. The tablet may be dissolved in less than about 20 ml or 15 ml of water.

The water-soluble active ingredient may have a solubility of at least 1 part in 30 parts of water at a neutral, acidic or alkaline pH. The therapeutic unit dose of the active ingredient may be soluble in about 30 ml of water in an acidic, alkaline or neutral pH. The water-soluble active ingredient may make up not more than 95% weight by weight of the tablet. The water-soluble active ingredient may be one or more of metformin hydrochloride, gabapentin, glibenclamide, glipizide, diltiazem hydrochloride, verapamil hydrochloride, bupropion hydrochloride, propranolol hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide hydrochloride, tramadol, fluoxetine hydrochloride, paroxetine hydrochloride, pentoxifylline hydrochloride, and diclofenac sodium. In particular, the water-soluble active ingredient may be metformin hydrochloride, a combination of metformin hydrochloride and glibenclamide, a combination of metformin hydrochloride and glipizide, or gabapentin.

The one or more sugar alcohols may be one or more of sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt, hydrogenated starch hydrolysates and combinations thereof. In particular, the sugar alcohol may be xylitol, mannitol, or a mixture of xylitol and mannitol.

The one or more water-soluble lubricants may be one or more of DL-leucine, sodium lauryl sulphate, magnesium lauryl sulphate and polyethylene glycol. In particular, the lubricant may be pulverized/micronised polyethylene glycol. The polyethylene glycol may have a particle size with 90% of the particles having a size less than 250 μm, a molecular weight of from about 3,500 to about 20,000, or a molecular weight of from about 3,500 to about 8,000.

The pH modifier may be one or more of potassium hydroxide, sodium hydroxide, monosodium citrate, citric acid and the like.

The tablet may further include one or more additional pharmaceutical excipients. The one or more additional pharmaceutical excipients may be one or more of binders, sweeteners, and flavouring agents. The binder may be one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s). The sweetener may be one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

In particular, the tablet may include one or more water-soluble active ingredients, xylitol, spray-dried mannitol and micronized polyethylene glycol and the tablet dissolves in about 30 ml of water within three minutes to give a clear solution.

In another general aspect there is provided a process for the preparation of a water-soluble tablet. The process includes compressing a mixture of (a) at least one water-soluble active ingredient; (b) one or more water soluble sugar alcohols; (c) one or more water-soluble lubricants; and (d) one or more pH modifiers. The tablet dissolves in about 3 minutes in about 30 ml of water to give a clear solution.

Embodiments of the process may include one or more of the following features or those described above. For example, the mixture may be formulated into a tablet by direct compression. The process may further include granulating the mixture prior to compression. The granulating may be wet granulation or dry granulation.

The one or more water-soluble active ingredients may be metformin hydrochloride, gabapentin, glibenclamide, glipizide, diltiazem hydrochloride, verapamil hydrochloride, bupropion hydrochloride, propranolol hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide hydrochloride, tramadol, fluoxetine

hydrochloride, paroxetine hydrochloride, pentoxifylline hydrochloride, and diclofenac sodium. The one or more water soluble sugar alcohols may be one or more of sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt and hydrogenated starch hydrolysates and combinations thereof. The one or more water-soluble lubricants may be one or more of DL-leucine, sodium lauryl sulphate, magnesium lauryl sulphate and polyethylene glycol. The one or more pH modifiers may be one or more of potassium hydroxide, sodium hydroxide, monosodium citrate, citric acid and the like.

The mixture may include additional pharmaceutical excipients. The additional pharmaceutical excipients may be one or more of binders, sweeteners, and flavouring agents. The binder may be one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s). The sweetener may be one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

In another general aspect there is provided a method of treating a condition. The method includes administering a water-soluble tablet that includes (a) at least one water-soluble active ingredient; (b) one or more water soluble sugar alcohols; (c) one or more water-soluble lubricants; and (d) one or more pH modifiers. The tablet dissolves in less than about three minutes in less than about 30 ml of water to give a clear solution.

Embodiments of the method may include one or more of the following features or those described above. For example, the one or more water-soluble active ingredients may be metformin hydrochloride, gabapentin, glibenclamide, glipizide, diltiazem hydrochloride, verapamil hydrochloride, bupropion hydrochloride, propranolol hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide hydrochloride, tramadol, fluoxetine hydrochloride, paroxetine hydrochloride, pentoxifylline hydrochloride, and diclofenac sodium. The one or more water soluble sugar alcohols may be one or more of sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt and hydrogenated starch hydrolysates and combinations thereof. The one or more water-soluble lubricants may be one or more of DL-leucine, sodium lauryl sulphate, magnesium lauryl sulphate and polyethylene glycol. The one or more pH modifiers comprises one or more of potassium hydroxide, sodium hydroxide, monosodium citrate, citric acid and the like.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have surprisingly discovered that a tablet having a pleasant taste, and that is capable of dissolving within three minutes in water without residual particulate matter, can be easily prepared through the use of water soluble sugar alcohols in the place of commonly used saccharides. The water-soluble sugar alcohols not only aid in the quick disintegration of the tablet but also provide compressible properties to the bulk. Sugar alcohols do not add moisture or contribute to moisture pickup and are chemically inert. These properties make sugar alcohols useful excipients for tablets because they protect water-sensitive active ingredients from degradation and do not react with the active ingredient. Additionally, sugar alcohols do not undergo the Maillard reaction and therefore do not discolor in the presence of free amines. In addition to the sugar alcohols, pH modifiers optionally may be added to formulations containing active ingredients that have poor solubility in neutral and acidic environments.

The inventors also have developed a process for preparing water-soluble tablets by direct compression of the one or more water-soluble active ingredients, one or more water-soluble sugar alcohols, one or more water-soluble lubricant, and, optionally, one or more pH modifiers. The process provides tablets that are rapidly soluble in aqueous media and provide an easy mode of administration. These tablets can also be swallowed like other conventional tablets.

The term "water-soluble tablet" as used herein means an uncoated tablet that dissolves in water, as described in the British Pharmacopoeia 1988, Vol. II. The solution produced may be slightly opalescent due to added substances used in the manufacture of the tablets.

The term "clear aqueous solution" as used herein means that the solution formed after the tablet has completely dissolved should appear transparent to the naked eye. However, the solution produced may be slightly opalescent due to some water-insoluble impurities present in the excipients used to make the tablets.

The term "water-soluble active ingredient" herein means an active ingredient having solubility of at least about 1 part in 30 parts of water. This term also includes those active ingredients in which 1 part of an active ingredient dissolves in more than 30 parts of water, but under acidic or alkaline conditions, the solubility is increased up to 1 part in 30 parts of water. The term "water-soluble active ingredient" also includes those active ingredients having a therapeutic unit dose in an amount that dissolves in about 30ml, in particular in about 20ml and more particularly in about 15 ml water in acidic, alkaline or neutral pH to give clear solution. The pH adjustment can be accomplished using acidic or basic pharmaceutical excipients.

Suitable water-soluble active ingredients include one or more of metformin hydrochloride, gabapentin, glipizide, glibenclamide, diltiazem hydrochloride, verapamil hydrochloride, bupropion hydrochloride, propranolol hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide hydrochloride, tramadol, fluoxetine hydrochloride, paroxetine hydrochloride, pentoxifylline hydrochloride, diclofenac sodium and the like. The water-soluble active ingredient may be present in an amount of up to about 95% weight by weight of the tablet.

Suitable water-soluble sugar alcohols include one or more of sorbitol, mannitol, spray-dried mannitol, xylitol, erythritol, isomalt and hydrogenated starch hydrolysates and combinations thereof. For example, xylitol and spray dried mannitol may be used. Suitable mannitol may be spray-dried mannitol, which is available under the trade name Pearlitol. Mannitol is a free flowing, directly compressible sugar alcohol that has a cooling taste due to a negative heat of solution. Mannitol also gives tablets good hardness and facilitates a quick dissolution. Spray dried mannitol has a particle shape that allows it to be free-flowing and easily mixed with other ingredients. These properties allow it to be used with high dose active ingredients that may exhibit flow problems. Mixing these typically difficult-to-compress active ingredients with spray-dried mannitol makes it possible to formulate a suitable tablet. The water-soluble sugar alcohol may be present in an amount of from about 10% to about 95% weight by weight of the tablet. For example, the water-soluble sugar alcohol may be present in amount of from about 30% to about 70% weight by weight of the tablet.

Suitable water-soluble lubricants include one or more of DL-leucine, sodium lauryl sulphate, magnesium lauryl sulphate and polyethylene glycol. For example, pulverized or

micronised polyethylene glycol, with 90% of the particles having a size that is less than 250 μm and a molecular weight that is from about 1500 to about 20,000 may be used. Polyethylene glycols having molecular weights of from about 3500 to about 8000 may also be used. The water-soluble lubricant may be present in an amount of from about 0.1% to about 10% weight by weight, and in particular, in an amount of from about 2% to about 10% weight by weight of the tablet.

Suitable pH modifiers include one or more of potassium hydroxide, sodium hydroxide, monosodium citrate, citric acid and the like.

Besides the active ingredient, water-soluble sugar alcohol(s) and water-soluble lubricant, the tablet may include one or more of binders, sweeteners and flavouring agents. Suitable binders include one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums, carboxyvinyl polymer(s) and combinations thereof. Suitable sweeteners include one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose. Suitable flavouring agents include one or more of strawberry aroma, raspberry aroma, cherry flavour, lime flavour, fruit extracts, citrates and tartarates.

The tablet can be prepared by any conventional tableting method. For example, in a direct compression method, the water-soluble active ingredient, one or more sugar alcohols, water-soluble lubricant, pH modifiers and other optional water-soluble excipients may be sifted through a mesh of suitable size. The sifted blend may be mixed with a water-soluble lubricant and compressed using suitable tooling.

In a wet granulation method, the active ingredient may be mixed with a binder and granulated with purified water. Alternatively, the water-soluble active ingredient may be mixed with one or more sugar alcohols, and optionally water-soluble lubricants, and granulated with a binder solution. The granules can be dried and mixed with other excipient(s) and water-soluble lubricants, and compressed using suitable tooling.

In a dry granulation method, the blend of all the ingredients can be compacted to make granules of suitable size, the resulting granules mixed with a water-soluble lubricant, and compressed.

Tablets are a preferred final dosage form, however, granules that include the water-soluble active ingredient and one or more water-soluble sugar alcohols, water-soluble lubricant, pH modifiers and other optional excipients can also be prepared and packed into sachets, bottles or other suitable packaging devices meant for unit/multiple dosage. These granules can be dissolved in water to give a clear solution and consumed.

The following examples illustrate water-soluble tablets of metformin and processes of making the compositions. The examples are merely provided to illustrate the compositions and processes for their preparation and are not intended to be limiting. The obvious variations of these compositions are contemplated to be within the scope of the present invention and the appended claims.

EXAMPLE 1

Tablets were formulated with the following ingredients:

	Amount per Tablet
Metformin Hydrochloride	500 mg
Spray-dried Mannitol	200 mg
Xylitol	200 mg
Aspartame	45 mg
Monosodium Citrate	20 mg
Micronized Polyethylene Glycol	25 mg

Process:

Metformin, spray-dried mannitol, xylitol, aspartame and monosodium citrate were sifted through a suitable mesh. Micronized polyethylene glycol was mixed with the above sifted blend and compressed into a tablet using the appropriate tooling. The tablets obtained, when dropped in 30 ml of water, dissolved quickly to give a clear solution.

EXAMPLE 2

Tablets were formulated with the following ingredients:

	Amount per Tablet
Metformin Hydrochloride	500 mg
Polyvinyl yrrolidone	10 mg
Spray-dried Mannitol	200 mg
Xylitol	200 mg
Aspartame	45 mg
Monosodium Citrate	20 mg,
Micronized Polyethylene Glycol	25 mg

Process:

Metformin hydrochloride and polyvinyl pyrrolidone were mixed in a blender and granulated with purified water. The granules were dried and mixed with spray-dried mannitol, xylitol, aspartame and monosodium citrate. The above blend was then mixed with the micronized polyethylene glycol and compressed using the appropriate tooling. The tablets obtained, when dropped in 30 ml of water, dissolved quickly to give a clear solution.

The compositions of Examples 1 and 2, prepared using metformin hydrochloride as the water-soluble active ingredient are listed in Table 1.

Table 1. Water-Soluble Tablets of Metformin Hydrochloride

Composition	Example 1	Example 2
Metformin hydrochloride	500mg	500mg
Polyvinyl pyrrolidone	--	10mg
Xylitol	200mg	200mg
Mannitol (spray-dried)	200mg	200mg
Aspartame	45mg	45mg
Monosodium citrate	20mg	20mg
Polyethylene glycol	25mg	25mg
Purified water	q.s.	q.s.
Total weight	**990mg**	**1000mg**

Additional exemplary tablet formulations are contemplated to use the water-soluble sugar alcohols described above and one or more water-soluble excipients, such as pH modifiers. Water-soluble tablets of gabapentin and metformin hydrochloride with glibenclamide can be prepared as disclosed in Tables 2 and 3, which correspond to Examples 3-5.

Table 2. Water-Soluble Tablets of Gabapentin

Composition	Example 3	Example 4
Gabapentin	600mg	600mg
Polyvinyl pyrrolidone	--	10mg
Xylitol	200mg	200mg
Mannitol (spray-dried)	200mg	200mg
Aspartame	45mg	45mg
Monosodium citrate	20mg	20mg
Polyethylene glycol	25mg	25mg
Purified water		q.s.
Total weight	**1090mg**	**1080mg**

Table 3. Water-Soluble Tablets of a Combination Product of Metformin Hydrochloride and Glibenclamide

Composition	Example 5
Metformin hydrochloride	500mg
Glibenclamide	5 mg
Polyvinyl pyrrolidone	10 mg
Xylitol	200 mg
Sodium hydroxide	5 mg
Mannitol (spray-dried)	170mg
Aspartame	.45mg
Saccharin sodium	5 mg
Flavors	30mg
Polyethylene glycol	30mg
Purified water	q.s.
Total weight	**1000 mg**

Glibenclamide has a poor solubility in neutral or acidic pH environments. In a basic environment, however, glibenclamide is more soluble. A pH modifier can be used to provide, for example, a more basic environment. Water-soluble tablets of metformin hydrochloride and glibenclamide including a pH modifier, namely, sodium hydroxide, were prepared. When the tablet was dropped in 30 ml of water, it dissolved quickly to give a clear solution. Although sodium hydroxide is exemplified here, other basic pH modifiers can be used instead and the use of sodium hydroxide merely exemplifies the concept. For example, suitable pH modifiers include potassium hydroxide, monosodium citrate, citric acid and the like.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations in the preferred methods of the present invention may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WE CLAIM:

1. A water-soluble tablet comprising:

(a) at least one water-soluble active ingredient;

(b) one or more water soluble sugar alcohols;

(c) one or more water-soluble lubricants; and

(d) one or more pH modifiers,

wherein the tablet dissolves in less than about three minutes in less than about 30 ml of water to give a clear solution.

2. The tablet according to claim 1, wherein the tablet dissolves in water within two minutes to give a clear solution.

3. The tablet according to claim 1, wherein the tablet dissolves in water within one minute to give a clear solution.

4. The tablet according to claim 1, wherein the tablet is dissolved in less than about 20 ml of water.

5. The tablet according to claim 1, wherein the tablet is dissolved in less than about 15 ml of water.

6. The tablet according to claim 1, wherein the water-soluble active ingredient has a solubility of at least 1 part in 30 parts of water at a neutral, acidic or alkaline pH.

7. The tablet according to claim 1, wherein the therapeutic unit dose of the active ingredient is soluble in about 30 ml of water in an acidic, alkaline or neutral pH.

8. The tablet according to claim 1, wherein the water-soluble active ingredient comprises not more than 95% weight by weight of the tablet.

9. The tablet according to claim 8, wherein the water-soluble active ingredient comprises one or more of metformin hydrochloride, gabapentin, glibenclamide, glipizide, diltiazem hydrochloride, verapamil hydrochloride, bupropion hydrochloride, propranolol hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide hydrochloride, tramadol, fluoxetine hydrochloride, paroxetine hydrochloride, pentoxifylline hydrochloride, and diclofenac sodium.

10. The tablet according to claim 1, wherein the water-soluble active ingredient comprises metformin hydrochloride.

11. The tablet according to claim 1, wherein the water-soluble active ingredient comprises a combination of metformin hydrochloride and glibenclamide.

12. The tablet according to claim 1, wherein the water-soluble active ingredient comprises a combination of metformin hydrochloride and glipizide.

13. The tablet according to claim 1, wherein the active ingredient comprises gabapentin.

14. The tablet according to claim 1, wherein the one or more sugar alcohols comprises one or more of sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt, hydrogenated starch hydrolysates and combinations thereof.

15. The tablet according to claim 14, wherein the sugar alcohol comprises xylitol.

16. The tablet according to claim 14, wherein the sugar alcohol comprises mannitol.

17. The tablet according to claim 14, wherein the one or more sugar alcohols comprises a mixture of xylitol and mannitol.

18. The tablet according to claim 1, wherein the one or more water-soluble lubricants comprises one or more of DL-leucine, sodium lauryl sulphate, magnesium lauryl sulphate and polyethylene glycol.

19. The tablet according to claim 18, wherein the water soluble lubricant comprises DL-leucine.

20. The tablet according to claim 18, wherein the water soluble lubricant comprises sodium lauryl sulphate.

21. The tablet according to claim 18, wherein the water soluble lubricant comprises magnesium lauryl sulphate.

22. The tablet according to claim 18, wherein the lubricant comprises pulverized/micronised polyethylene glycol.

23. The tablet according to claim 22, wherein the polyethylene glycol has particle size with 90% of the particles having a size less than 250 μm.

24. The tablet according to claim 23, wherein the polyethylene glycol has a molecular weight of from about 3,500 to about 20,000.

25. The tablet according to claim 24, wherein the polyethylene glycol has a molecular weight of from about 3,500 to about 8,000.

26. The tablet according to claim 1, wherein the pH modifier comprises one or more of potassium hydroxide, sodium hydroxide, monosodium citrate, citric acid and the like.

27. The tablet according to claim 1, wherein the tablet further comprises one or more pharmaceutical excipients.

28. The tablet according to claim 27, wherein the pharmaceutical excipients comprise one or more of binders, sweeteners, and flavouring agents.

29. The tablet according to claim 28, wherein the binder comprises one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s).

30. The tablet according to claim 28, wherein the sweetener comprises one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

31. The tablet according to claim 1, wherein the tablet comprises one or more water-soluble active ingredients, xylitol, spray-dried mannitol and micronized polyethylene glycol and the tablet dissolves in about 30 ml of water within three minutes to give a clear solution.

32. A process for the preparation of a water-soluble tablet, the process comprising compressing a mixture of:

(a) at least one water-soluble active ingredient;

(b) one or more water soluble sugar alcohols;

(c) one or more water-soluble lubricants; and

(d) one or more pH modifiers,

wherein the tablet dissolves in about 3 minutes in about 30 ml of water to give a clear solution.

33. The process according to claim 32, wherein the mixture is formulated into a tablet by direct compression.

34. The process according to claim 32, further comprising granulating the mixture prior to compression.

35. The process according to claim 34, wherein the granulating comprises wet granulation.

36. The process according to claim 34, wherein the granulating comprises dry granulation.

37. The process according to claim 32, wherein the one or more water-soluble active ingredients comprises metformin hydrochloride, gabapentin, glibenclamide, glipizide, diltiazem hydrochloride, verapamil hydrochloride, bupropion hydrochloride, propranolol hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide hydrochloride, tramadol, fluoxetine hydrochloride, paroxetine hydrochloride, pentoxifylline hydrochloride, and diclofenac sodium.

38. The process according to claim 32, wherein the one or more water soluble sugar alcohols comprises one or more of sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt and hydrogenated starch hydrolysates and combinations thereof.

39. The process according to claim 32, wherein the one or more water-soluble lubricants comprises one or more of DL-leucine, sodium lauryl sulphate, magnesium lauryl sulphate and polyethylene glycol.

40. The process according to claim 32, wherein the one or more pH modifiers comprises one or more of potassium hydroxide, sodium hydroxide, monosodium citrate, and citric acid.

41. The process according to claim 32, wherein the mixture comprises additional pharmaceutical excipients.

42. The process according to 41, wherein the additional pharmaceutical excipients comprise one or more of binders, sweeteners, and flavouring agents.

43. The process according to claim 42, wherein the binder comprises one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s).

44. The process according to claim 42, wherein the sweetener comprises one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

45. A method of treating a condition, the method comprising administering a water-soluble tablet comprising:

(a) at least one water-soluble active ingredient;

(b) one or more water soluble sugar alcohols;

(c) one or more water-soluble lubricants; and

(d) one or more pH modifiers,

wherein the tablet dissolves in less than about three minutes in less than about 30 ml of water to give a clear solution.

46. The method according to claim 45, wherein the one or more water-soluble active ingredients comprises metformin hydrochloride, gabapentin, glibenclamide, glipizide, diltiazem hydrochloride, verapamil hydrochloride, bupropion hydrochloride, propranolol hydrochloride, dextromethorphan hydrobromide, diphenhydramine hydrochloride, disopyramide hydrochloride, tramadol, fluoxetine hydrochloride, paroxetine hydrochloride, pentoxifylline hydrochloride, and diclofenac sodium.

47. The method according to claim 45, wherein the one or more water soluble sugar alcohols comprises one or more of sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt and hydrogenated starch hydrolysates and combinations thereof.

48. The method according to claim 45, wherein the one or more water-soluble lubricants comprises one or more of DL-leucine, sodium lauryl sulphate, magnesium lauryl sulphate and polyethylene glycol.

49. The method according to claim 45, wherein the one or more pH modifiers comprises one or more of potassium hydroxide, sodium hydroxide, monosodium citrate, and citric acid

INTERNATIONAL SEARCH REPORT

International Application No
.../IB2004/001104

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/155 A61K31/196 A61K31/198 A61K31/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 39 09 520 A (CIBA GEIGY AG) 5 October 1989 (1989-10-05) column 1, line 57 - column 2, line 7 column 3, line 16 - column 5, line 58; example 9	1-9,18, 22-29, 32-37, 39-43
Y		10-17, 19-21, 30,31,44
Y	US 6 284 275 B1 (CHENG XIU XIU ET AL) 4 September 2001 (2001-09-04) column 2, lines 40-58; example 1	10-17, 19-21, 30,31,44
X	GB 1 248 190 A (BRISTOL-MYERS) 29 September 1971 (1971-09-29) the whole document	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2004	21/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uhl, M

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/IB2004/001104

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 45-49
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
/IB2004/001104

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